REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 20-64 are in this case. Claims 22-26 and 35-38 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 20-21, 27-34, 39-64 have been rejected. Claim 41 and 44 have now been canceled. Claims 20 and 45-51 have now been amended. New claims 65-69 have now been added.

Request for New Declaration

The Examiner states that a handwritten change found in the specification at page 50 requires a new declaration. Applicant is in the process of attending to this issue.

35 U.S.C. § 112, Second Paragraph Rejection

The Examiner has rejected claims 20-21, 27-34 and 39-64 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner's rejections are respectfully traversed. Claims 20 and 45-51 have now been amended. Claim 44 has now been canceled, rendering moot the Examiner's rejection of this claim.

The Examiner explicitly concedes that the specification describes minimal signs of acute graft-versus-host disease as being grade I/II mucocutaneous graft-versus-host disease involving the skin and oral cavity without intestinal or liver involvement. Nevertheless, the Examiner contends that the phrase "minimal graft-versus-host disease" is vague and indefinite based on the Examiner's contention that it has not been adequately defined in the specification.

Applicant remains of the very strong opinion that the specification's description of "minimal (signs of acute) graft-versus-host disease" as grade I/II mucocutaneous graft-versus-host disease involving the skin and oral cavity without intestinal or liver involvement indeed constitutes a very clear and adequate definition of minimal graft-versus-host disease amply fulfilling the 35 U.S.C. § 112, Second Paragraph clarity and definiteness requirements. Applicant wishes to further point out that the Examiner has failed to address Applicant's arguments and supporting

documents in Applicant's response to the Office Action mailed July 7, 2003 which clearly establish that minimal graft-versus-host disease, as recited in the specification, was in fact well defined in the art, and was commonly understood by one of ordinary skill in the art at the time of the invention.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant has now amended claim 20 to now include the now cancelled claim 44 limitation of graft-versus-host disease having a grade selected from a range of grade I to grade II, and to amend claims 45-51 to respectively to limit said graft-versus-host disease to graft-versus-host disease which: (i) is mucocutaneous; (ii) involves the oral cavity; (iii) involves the skin; (iv) does not substantially involve the intestines; (v) does not substantially involve the liver; (vi) is acute; and (vii) is chronic.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 112, First Paragraph Rejection

The Examiner has rejected claims 20-21, 27-34 and 39-64 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claim 20 has now been amended. New claims 65-69 have now been added. Claim 41 has now been cancelled rendering moot the Examiner's rejection thereof.

In particular, the Examiner contends that the specification and the claims as originally filed do not provide support for the invention claimed as:

"*A method of treating a human cancer patient, the patient having undergone a malignant cell debulking procedure associated with at least partial loss of hematopoiesis, and having further undergone autologous stem cell transplantation incident to the debulking procedure, the patient being at risk of disease relapse due to a population of residual malignant cells that may remain viable in the patient following the debulking procedure, the method comprising:*

(a) administering to the patient a dose of lymphocytes derived from a lymphocyte donor in a regimen selected so as to cause at least partial

engraftment of said lymphocytes in the patient, said lymphocyte donor being allogeneic with the patient; and

(b) administering to the patient a dose of stem cells derived from a stem cell donor in a regimen selected so as to cause minimal graft-versus-host disease (GVHD) in the patient, said stem cell donor being allogeneic with the patient, thereby treating the cancer in the patient."

With respect to Applicant's pointing out that the support for the new method is found at pages 37-38 regarding Patient No. 8, the Examiner contends that such disclosure of a specific example is insufficient to support generic independent claims. The Examiner contends that, for example, the claim would encompass the treatment of any cancer patient, but that the example discloses only the treatment of one patient having a specific malignancy. The Examiner further contends that the method as claimed in Applicant's response to the Office Action mailed July 7, 2003 is not that disclosed in the as the generic method of the specification. The Examiner bases the latter contention on the grounds that the specification at page 18 teaches that the claimed method is intended to encompass only temporary engraftment because permanent engraftment would put the patient at risk of severe graft-versus-host disease. The Examiner further bases such contention on the grounds that the specification at page 23 discloses that engraftment of immunocompetent T-lymphocytes from a donor could cause graft-versus-host disease which could be stormy and lethal, whereas new Claim 41 recites a method encompassing full engraftment of the donor lymphocytes. The Examiner contends that accordingly all of the claims under examination comprise new matter.

Applicant vigorously disagrees with the Examiner's contention that the specification and the claims as originally filed do not support the invention as claimed above.

With respect to the Examiner's contention that disclosure of a specific example (Patient No. 8 having a hematopoietic malignancy) is insufficient to support generic independent claims, Applicant wishes to respectfully point out that in fact it is widely established in the art that many different types of malignancies, in particular many different types of hematopoietic malignancies, respond to highly similar or identical therapies, in particular therapies involving administration of allogeneic cells (refer, for example, to underlined passages in enclosed abstracts of Akpek, 2002;

Gratwohl A, 1996; Santos, 1984; and Toren, 1995), such as that those taught by the present invention. As such, Applicant is of the very strong opinion that the specific example provided in the specification can indeed be broadly generalized to various types of malignancies. Nevertheless, in the interest of expediting prosecution of the instant application, Applicant has now amended claim 20 to now limit the human cancer patient to one which has a hematological malignancy; to add new Claims 65-67, respectively limiting the hematopoietic malignancy to a lymphoma, a B-cell lymphoma or a non-Hodgkin's B-cell lymphoma; and to add new Claim 68 limiting the human cancer patient to one which is an adult. Therefore, since, as described hereinabove, numerous hematopoietic malignancies are treatable via highly similar or identical treatments involving administration of allogeneic hematopoietic cells, Applicant believes limiting the cancer to a hematopoietic malignancy overcomes the Examiner's rejections which are based on Applicant's referral to Patient No. 8 to exemplify the claimed method.

Applicant is of the strong opinion that the grounds upon which the Examiner bases the contention that the method as claimed in Applicant's response is not that disclosed as the generic method are clearly unfounded. Namely, with respect to the Examiner's contention that the specification at page 18 teaches that the claimed method is intended to encompass only temporary engraftment because permanent engraftment would put the patient at risk of severe graft-versus-host disease, Applicant wishes to respectfully point out that the relevant passage of page 18 is clearly speculative, non-limiting and essentially irrelevant by virtue of reciting at lines 6-10: "*following administration of allogeneic lymphocytes... temporary engraftment of allogeneic effector cells may be sufficient to induce beneficial GVL effects, without the need for permanent residence of allogeneic effector cells, which may put the patient at risk for severe GVHD...*". Specifically, such uses of the term "*may*" very clearly indicate that permanent engraftment of allogeneic effectors are acceptable in certain circumstances, such as when practicing the method exemplified by Patient No. 8. Applicant wishes to respectfully point out that the Examiner's contention that the specification at page 23 discloses that engraftment of immunocompetent T-lymphocytes from a donor could cause stormy and lethal graft-versus-host disease is incorrect when practicing the method exemplified by Patient No. 8. Namely, the relevant passages (paragraph starting at line 7) are in fact a description of the prior art

and are not provided as guidelines for practicing any aspect of the present invention. That the cited paragraph is a description of the prior art is readily apparent since the paragraph starting at line 7 refers to "*normal circumstances*" of the prior art wherein "*recipients receive only irradiated blood products*", whereas by explicit contrast the following paragraph, at line 19, recites "*In the method of the present invention, non-irradiated donor-type lymphocytes are used intentionally for induction of graft-versus-malignant cell effects that may be accompanied by mild GVHD*". Applicant wishes to point out that the method exemplified by Patient No. 8 in fact teaches, over the prior art as described at page 23, engraftment of allogeneic donor bone marrow derived effector cells which do not cause stormy and lethal graft-versus-host disease. Applicant wishes to strongly emphasize that the method exemplified by Patient No. 8 is indeed encompassed by the generic method of the specification as formulated by the Examiner, in sharp contrast to the Examiner's contention that it is not. Namely, the method exemplified by Patient No. 8 is indeed effected by administering to the patient allogeneic lymphocytes (specification, page 37, sentence starting at line 16) which do not permanently engraft (specification, page 38, sentence starting at line 1). The method exemplified by Patient No. 8 merely includes the additional step of administering allogeneic bone marrow cells subsequent to administration of the allogeneic lymphocytes (specification, page 38, sentence starting at line 11). The Examiner's page 18 citation, by virtue of referring to graft-versus-host disease resulting from direct administration of allogeneic lymphocytes as opposed to that resulting from administration of allogeneic bone marrow cells is essentially irrelevant due to the significant differences in the immunological effects resulting from such different types of allogeneic cell administration. Namely, as taught in the method exemplified by Patient No. 8, administration of donor allogeneic bone marrow following that of transiently engrafted allogeneic donor lymphocytes can result in engraftment of donor allogeneic effectors which, as described above, do not cause "stormy and lethal" graft-versus-host disease, but rather beneficial and controllable grade I/II graft-versus-host disease. It is indeed well known in the art that administration of allogeneic donor bone marrow cells can have potent immunomodulatory effects, such as induction of tolerization to subsequent donor grafts, which are very different from those resulting from administration of allogeneic lymphocytes. Thus, Applicant is of

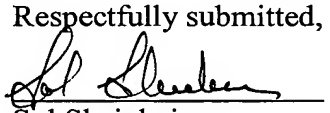
the very strong opinion that clearly the method exemplified by Patient No. 8 is merely a specific embodiment of the generic method of the present invention which includes an additional step of allogeneic bone marrow cell administration.

Nevertheless in the interest of expediting prosecution of the instant application, Applicant has (i) amended claim 20 to now include the limitation of administering to the patient a dose of stem cells derived from a stem cell donor subsequent to administration of the lymphocyte dose; (ii) amended claim 20 to replace the recitation of at least partial engraftment with that of partial engraftment (iii) cancelled claim 41 limiting the at least partial engraftment to full engraftment; and (iv) added new Claim 69 including the limitation of said regimen selected to cause GVHD being further selected so as to cause permanent engraftment of said dose of stem cells.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

In view of the amendments and remarks set forth above it is respectfully submitted that claims 20-21, 27-34, 39-40, 42-43 and 45-69 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein
Registration No. 25,457

Date: June 15, 2004

Encls.:

A response transmittal fee for added claims;
Abstract of Akpek G. Leuk Lymphoma. 2002 Jun;43(6):1211-20;
Abstract of Gratwohl A. Ther Umsch. 1996 Feb;53(2):152-7;
Abstract of Santos GW. Cancer. 1984 Dec 1;54(11 Suppl):2732-40; and
Abstract of Toren A. *et al.*, Med Oncol. 1995 Sep;12(3):177-86.

Leuk Lymphoma. 2002 Jun;43(6):1211-20. Related Articles, Links

MetaPress

Clinical grading in chronic graft-versus-host disease: is it time for change?

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Many hematologic disorders, leukemias and lymphomas in particular, can be cured with allogeneic hematopoietic stem cell transplantation (allo-SCT). However, chronic graft-versus-host disease (cGVHD) appears to remain as a major determinant of long term outcome and quality of life following allo-SCT. The gradual increase in the incidence of cGVHD over the past decade has recently gained another momentum along with the use of blood as a source of stem cells. Donor lymphocyte infusion (DLI) is also associated with a progressive form of cGVHD, mostly refractory to treatment. Prediction of the outcome of patients with newly diagnosed chronic GVHD may be important in identifying those who are likely to benefit from reduced treatment and patients who are unlikely to have a sustained response to standard treatment. In addition, a reliable predictive model could allow us to design better clinical trials and facilitate the communication among the centers. Although it is highly reproducible, the current system of grading in cGVHD is of limited utility since it does not stratify patients for outcome. It divides patients into those needing treatment (extensive cGVHD) and those who do not (limited cGVHD). Therefore, a new clinical grading system is needed to classify all patients based on their prognosis so like patients with similar features can be grouped for study and clinical management purposes. Using multivariate analysis, we recently identified three independent risk factors affecting the survival without recurrent malignancy. These factors are extensive skin involvement (>50% BSA), thrombocytopenia, and progressive-type onset of cGVHD. We are in the process of validating this prognostic model in three other cohorts from different institutions. We expect that the new grading system, based on this model, may allow us to identify the diversity of outcome within "extensive stage" cGVHD.

Publication Types:

- Review
- Review, Multicase

PMID: 12152988 [PubMed - indexed for MEDLINE]

Ther Umsch. 1996 Feb;53(2):152-7.

[Indications for bone marrow and peripheral stem cell transplantation in malignant hematological diseases]

[Article in German]

Gratwohl A.

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Transplantation of hematopoietic precursor cells is an established therapy today in the treatment of hematological malignancies. Cells from different sources [bone marrow, peripheral blood, cord blood] and from different donor types [autologous, syngeneic or allogeneic] are used for transplantation. The aim of autologous transplantation is to apply intensive high-dose chemo-radiotherapy and to shorten the duration of aplasia. Allogeneic cells, in addition, are free of potentially contaminating precursor cells and provide a graft-versus-leukemia effect. For all patients, transplantation should be considered at diagnosis as an integral part of treatment strategy and, depending on risk factors, be performed early in the course of disease. Preferred time for patients with high-risk acute leukemias is first complete remission, second complete remission for standard or low-risk acute leukemias. For chronic myeloid leukemia, allogeneic transplantation should be performed within one year of diagnosis, preferably still in first chronic phase. Autologous transplantation can be considered in a protocol setting. For patients with myelodysplastic syndromes of the FAB subtype refractory anemia or refractory anemia with sideroblasts, allogeneic transplantation is the treatment of choice as initial therapy. For patients with refractory anemia and excess of blasts with or without transformation, remission induction should be attempted before transplantation. Autologous transplantation is the preferred treatment strategy for patients with Hodgkin's and non-Hodgkin's lymphoma, for high-risk patients in first complete remission, for other patients in chemotherapy-sensitive first relapse. For patients with myeloma, transplantation should be considered after first line therapy. Age is the main individual patient's risk factor, transplant-related mortality immediately increases in parallel to increasing age. Autologous transplants are limited to patients below 60 to 65 years, allogeneic HLA-identical sibling transplants to patients below 50 to 55 years, and unrelated transplants to patients below 40 to 45 years. Prerequisites for transplant are availability of a donor, access to a transplant bed, informed consent of patient and donor, as well as financial guarantee. Indications for the different hematological malignancies and the major risk factors are discussed.

Publication Types:

- Review
- Review, Tutorial

PMID: 8629266 [PubMed - indexed for MEDLINE]

Cancer. 1984 Dec 1;54(11 Suppl):2732-40. Related Articles, Links

Bone marrow transplantation in leukemia. Current status.

Santos GW.

Intensive cytoreductive therapy may be curative in certain hematopoietic malignancies, but its administration is limited by lethal marrow toxicity. Bone marrow transplantation (BMT) provides a way of rescue from this toxicity. The donor may be a human leukocyte antigen (HLA) "matched" sibling (allogeneic), an identical twin (syngeneic), or the patient (autologous). Long remissions and possible cures of 50% to 60% have been reported in acute leukemia after intensive treatment with chemotherapy, with and without total body irradiation, followed by allogeneic BMT. A similar approach has been used in chronic myelocytic leukemia (CML) and in non-Hodgkin's lymphoma with encouraging results. Results are best in younger patients and those transplanted early in their disease (i.e., in the first remission for acute leukemia and in the chronic phase of the disease in CML). Solutions to major problems associated with allogeneic BMT, such as graft-versus-host disease and viral infections, are being actively pursued. Syngeneic BMT avoids some of the above problems, but relapses appear to be greater. Nevertheless, this approach has produced a significant number of cures. Autologous BMT is the newest approach, and the demonstration that marrow may be purged of residual tumor cells by immunologic or pharmacologic means has engendered enthusiasm for this area of clinical therapeutic investigation.

Publication Types:
- Review

PMID: 6388815 [PubMed - indexed for MEDLINE]

Med Oncol. 1995 Sep;12(3):177-86.

Related Articles, Links

Role of interleukin-2 in human hematological malignancies.

Toren A, Ackerstein A, Slavin S, Nagler A.

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Clinical studies with Interleukin-2 (IL-2) in human hematologic malignancies were initiated in the late 1980s. Based on clinical studies on various solid tumors, and laboratory research on hematopoietic cells, IL-2 was shown to be effective in 150 acute myeloid leukemia (AML) patients mainly for maintenance therapy in first complete remission, or with residual blast cells in the marrow. IL-2 has also been shown to be effective in remission induction in 10 patients with chronic myeloid leukemia (CML). The role of IL-2 in lymphoma patients remains to be established. IL-2 alone or in combination with Interferon-alpha, may intensify remission and prolong disease-free survival when given post autologous bone marrow transplantation (BMT) to patients with lymphoma and myeloid leukemia, and to a lesser degree, to patients with acute lymphatic leukemia (ALL). IL-2 in combination with HLA-matched or mismatched peripheral blood lymphocytes was also used post autologous BMT in preliminary studies. IL-2 was administered with or without peripheral blood lymphocytes, for prevention of relapse post T-cell-depleted allogeneic BMT in CML, ALL and AML, with encouraging results. The same strategy was shown to be effective in the reinduction of remission in patients with CML, who relapsed post BMT.

Publication Types:

- Review
- Review, Tutorial

PMID: 8852400 [PubMed - indexed for MEDLINE]